Remarks

Claims 2 and 12-49 are pending. Claims 2, 12-33, 35, 36, 40, and 46-49 have been amended. Claims 2-11 have been canceled. Claims 41-45 stand withdrawn as being drawn to a non-elected invention.

Support for amended claims 2, 12-33, 35, 36, 40, and 46-49 comes at least from the original claims as filed. Applicants have amended the claims to facilitate prosecution, but maintain that the claims were clear and unambiguous as drafted before because the claims made clear that there was only one nucleic acid molecule and one "target nucleic acid molecule." This is so because the "nucleic acid molecule" has an activity, while the target nucleic acid molecule is uniquely identified with "target."

Rejection under 35 U.S.C. § 112, second paragraph

Applicants have amended claims 2, 12-33, 35, 36, 40, and 46-49 which moots the objection of claims 12-49 under 35 U.S.C. § 112, second paragraph. Applicants respectfully traverse this objection.

Rejection under 35 U.S.C. § 112, first paragraph

Claim 40 was rejected under 35 U.S.C. § 112, first paragraph, on the basis that the specification, while being enabling for ribozyme-mediated cleavage of mRNA *in vitro*, allegedly does not reasonably provide enablement for ribozyme-mediated cleavage of mRNA specifically for pharmaceutical compositions *in vivo*, or for methods of treating diseases associated with its expression *in vivo*. Applicants traverse this rejection.

The present rejection cannot be maintained at least because the rejection is based on an incorrect legal standard for enablement, claim 40 is enabled under the correct legal standard, and the publications cited in the rejection actually support enablement of claim 40 under the correct legal standard.

A. The Legal Standard For Enablement

Any analysis of whether a particular claim is enabled by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. The test of enablement is whether one skilled in the art could make or

use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343, 199 USPQ 659 (CCPA 1976). A patent need not teach, and preferably omits, what is well known in the art. *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 3 USPQ2d 1737 (Fed. Cir. 1987). Determining enablement is a question of law based on underlying factual findings. *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991); Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984).

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.I.T. v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt,* 537 F.2d 498, 190 USPQ 214 (CCPA 1976).

1. Enablement of Pharmaceutical Compositions

The standard for use[1] does not change if the subject matter is pharmaceutical or therapeutic in nature. *In re Chilowsky*, 229 F.2d 457, 461-2 (CCPA 1956). "Knowledge of pharmacological activity is an obvious benefit to the public. . . . [A]dequate proof of any such activity constitutes a showing of practical utility" *Nelson v. Bowler*, 626 F.2d 853, 856 (CCPA 1980). The Federal Circuit held that adequate proof of a pharmacological activity can be obtained by merely providing *in vitro* data which is *suggestive* of an activity *in vivo*. *Cross v. Iizuka*, 753 F.2d 1040 (Fed. Cir. 1985) (emphasis added). "Successful in vitro testing . . . [will lead to] . . . in vivo testing . . . thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an in vivo utility." *Id.* at 1051. Future testing in animals and future testing in humans, even if extensive, does not prevent a specification from

[1] Whether the utility requirement comes from 35 U.S.C. § 101 or 35 U.S.C. § 112, the standard to be applied is the same. Ex parte Maas, 14 USPQ2d 1762, 9 USPQ2d 1746, 1747 (Bd. Pat. App. & Int'f 1987). The Maas court stated, "the issue under 35 U.S.C. § 112 relating to an enabling disclosure is subsumed within the issue under 35 U.S.C. § 101 relating to patentable utility." Any analysis of a claim under 35 U.S.C. § 112, first paragraph, relating to the use of the claimed subject matter need only meet the standards of the utility requirement of 35 U.S.C. § 101 because if the claimed subject matter meets the utility requirement it is presumed to meet the enablement requirement.

meeting the utility requirement. The court stated in *In re Brana*, "Usefulness in Patent law and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development." *In re Brana*, 51 F.3d 1560, 1568 (Fed. Cir. 1995). If the subject matter covered by pharmaceutical inventions requires future research and development, even after conception and constructive reduction to practice, when then is the utility requirement met? The Federal Circuit has answered this question: "The stage at which an invention in this field becomes useful [i.e. enabled with respect to use requirement] is *well before* it is ready to be administered to humans." (emphasis added). *Id.* at 1568.

The law does not explicitly state what is required to meet the use requirement for any given pharmacological use because an analysis of utility is a fact based decision. *Ratheon v. Roper*, 724 F.2d 956. The law is explicitly clear, however, as to what pharmaceutical use does not require. Pharmaceutical use does not require human testing.[2] Pharmaceutical use does not require animal testing.[3] Pharmaceutical use does not require a showing of therapeutic safety.[4] Most importantly, pharmaceutical use does not require a showing of efficacy.[5]

B. The Specification Provides In Vitro Data Suggestive of Activity In Vivo

There is no dispute that the nucleic acid molecules having endonuclease activity of claim 40 are functional in vitro. The specification provides *in vitro* data to show this and the rejection does not dispute that the molecules have demonstrated activity. Applicants submit that the in vitro activity of the claimed molecules is suggestive of in vivo activity for these molecules, which is all that is required for an enabled use of pharmaceutical composition under the legal standard discussed above. In particular, the activity data in the specification is the type of data

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[2] *In re Jolles*, 628 F.2d 1322 (CCPA, 1980); *In re Krimmel*, 292 F.2d 948 CCPA, 1961); *Cross v. Iizuka*, 753 F.2d 1040 (1985); and *In re Brana* 51 F.3d 1560 (Fed. Cir. 1995).

[3] *In re Krimmel*, 292 F.2d 948 CCPA, 1961) and *Cross v. Iizuka*, 753 F.2d 1040 (1985).

[4] *In re Brana* 51 F.3d 1560 (Fed. Cir. 1995) and *In re Irons*, 340 F.2d 974, 978 CCPA 1965).

[5] See *In re Sichert*, 566 F.2d 1154, 196 USPQ 209 (1977); I*n re Hartop*, 311 F.2d 249, 135 USPQ 419 (CCPA 1962); *In re Anthony*, 414 F.2d 1383, 162 USPQ 594 (CCPA 1969); *In re Watson*, 517 F.2d 465, 186 USPQ 11 (CCPA 1975); *In re Krimmel*, 292 F.2d 948, 130 USPQ 215 (CCPA 1961); *Ex parte Jovanovics*, 211 USPQ 907 (Bd. Pat. App. & Inter. 1981).

sufficient to move the molecules forward in the drug development process. The specification clearly shows that the claimed nucleic acid molecules have high affinity and activity for target substrates (see for example, Example 5 of the specification). This is the type of activity which would be "suggestive" of activity *in vivo*. This is all that is required by *Cross v Iizuka*. Accordingly, for at least these reasons, claim 40 is fully enabled.

C. The Rejection Relies On An Incorrect Legal Standard

The present rejection is improperly based on a high level of *efficacy in vivo*. Applicants assert that even for the therapeutic uses at issue, applicants are not required to support or demonstrate some arbitrary level of use or effectiveness. All that is required is that the claimed compositions work to some extent and that this minimal level of use is enabled. For example, it is not required that the claimed compositions cure any disease, prolong life, or even cleave a certain number of target nucleic acids. All that is required is that the claimed compositions, at a minimum, target the cleavage of a single substrate in a single cell. Applicants assert that there can hardly be any question that the claimed compositions will accomplish this. Contrary to the implication of the rejection and as discussed above, the "use" of the claimed compositions enabled by the specification need not be a commercially viable therapeutic or even a therapeutically efficacious treatment.[6] Applicants are not required to demonstrate a safe and effective therapeutic, especially when the claims do not require such a capability. The question of whether a molecule is efficacious in, for example, treating a disease, is the domain of the Food and Drug administration, not the PTO. The courts have clearly indicated that molecules are ready for patenting well before they are ready for administration to humans. See e.g. *In re Brana*, 51 F.3d 1560, 1568 (Fed. Cir. 1995).

[6]see *In re Langer*, 183 USPQ 288, 298 (CCPA 1974) (full scale clinical trials in humans...may be necessary to establish 'commercial usefulness' in this technology. However, development of a product to the extent that it is commercially salable in the marketplace is not required to establish 'usefulness'); see also *Ex parte Maas*, 14 USPQ2d 1762, 9 USPQ2d 1746, 1747 (Bd. Pat. App. & Int'f 1987) (appeal presents "only one issue...whether [applicants] have provided substantiating evidence...to establish that the subject matter defined [in the claims] possesses a practical utility"; "the issue under 35 USC 112 relating to an enabling disclosure is subsumed within the issue under 35 USC 101 relating to patentable utility"); *In re Hafner*, 410 F.2d 1403, 1405, 161 USPQ 783, 785 (CCPA 1969) ("The disclosure of how to use must relate to a use of the kind considered by the Supreme Court in Brenner v. Manson to be a sufficient utility.").

The rejection and the evidence relied on in the rejection clearly focus on "curing a patient." The rejection states, "[s]ince the specification fails to provide any guidance for the successful treatment or prevention of any disease . . . ," when concluding the argument. This is not the standard (see footnote 5 above for federal court cases holding that therapeutic efficacy is not required nor part of the standard for enablement). The standard requires only that the data provided *suggest* that the molecule could work *in vivo*. Treating, efficacy, and curing fall outside the appropriate standard. The publications relied on in the rejection and how the sections in these publications are relied on clearly focus on the wrong standard, i.e. efficacy.

D. The Evidence Relied On Does Not Support The Correct Legal Standard

The rejection cites several publications as allegedly supporting the rejection. These publications are Gewirtz et al., "Facilitating oligonucleotide delivery: Helping antisense deliver on its promise," Proc. Natl. Acad. Sci. U.S.A., 93:3161-3163 (April, 1996) ("Gewirtz"); Tamm et al., "Antisense therapy in oncology: new hope or old idea," The Lancet, 358:489-497 (2001) ("Tamm"); Braasch and Corey, "Novel Antisense and Peptide nucleic acid strategies for controlling gene expression," 41(14):4503- 4510 (2002) ("Braasch"); Agrawal, "Antisense oligonucleotides: towards clinical trials," TIBTech, 14:376-387 (1996) ("Agrawal"); and Branch, "A good antisense molecule is hard to find," TIBS, 23:45-50 (1998) ("Branch").

As discussed below, Gewirtz, Tamm, Braasch, Agrawal, and Branch on the whole *support* the enablement of present claim 40 because even though these articles focus on antisense which is not the subject matter of claim 40, each of these articles teach: (1) that antisense oligonucleotides can and do work in vivo at some level, (2) that in the field of therapeutic oligonucleotides screening for molecules that bind *in vivo* is an expected, accepted, and easily achieved aspect of the technology, and (3) that *in vitro* assays are suggestive of *in vivo* activity.

1. Braasch

The rejection relied on Braasch to show (1) that the field of antisense oligomers is not predictable, (page 3 and 4, Office Action of July 29, 2003) and (2) that there are non-specific toxic effects of *in vivo* antisense administration (page 5, Office Action, July 29, 2003).

Applicants first note that Braasch involves "antisense" oligonucleotides, not nucleic acid molecules having endonuclease activity, and thus is not directly relevant to claim 40. The

nucleic acid molecules with endonuclease activity of claim 40 do not rely on the same mechanism of action that antisense molecules rely on. To the extent results with antisense molecules are relevant to the nucleic acid molecules of claim 40, Braasch provides evidence that therapeutic oligonucleotides can function *in vivo*. In fact, Braasch discusses the success of clinical trials of multiple antisense oligonucleotides (see for example, Table 1, which lists multiple antisense oligonucleotides that are "approved or in the clinic"). Braasch ends the article stating, "Experience in the clinic is demonstrating that even older generation oligonucleotide designs are effective drugs, and a detailed database of pharmacological information is being developed." (Braasch, 4509, col.2). Thus, Braasch clearly supports that therapeutic oligonucleotides can have *in vivo* activity because Braasch indicates the much higher standard of therapeutic efficacy has already been achieved by antisense molecules. As discussed above, only minimal activity is required for enablement.

Regarding the non-specific toxic effects discussed in Braasch, such effects are not relevant to the claimed nucleic acid molecules (and, as discussed below, not relevant to enablement in any sense). The nucleic acid molecules of claim 40 have far more specificity than any antisense molecule could have because they do not rely on simply a contiguous stretch of Watson-Crick interaction for activity, like antisense molecules do. The nucleic acid molecules of claim 40 require that there be a stretch of bases which can base pair with the X arm of the nucleic acids of claim 40, separated by a very specific sequence, GG, which is not bound in a Watson-Crick manner, by the hybridizing sequence, and then another stretch of bases which can base pair with the Y arm of the nucleic acids of claim 40. Thus, the very problems worried about in, for example, Braasch and Branch, that you cannot increase the specificity of antisense oligos because a certain amount of bases is required for specificity (for example 20), but by using this many bases, many smaller, for example, 10 mers or 11 mers will have a chance of binding and causing non-specific antisense effects is not an issue with the claim 40 molecules. In the nucleic acid molecules with endonuclease activity of claim 40, the hybridizing arms, can for example, be smaller than for example, 11 or 12, thus decreasing the chance of non specific binding, but because of how the enzymes interact with the subject, they will actually have an affinity for the desired target similar to an antisense molecule having many more than 10 contiguous bases (this

is because of the two separate hybridizing arms, each adding to the specific affinity of the claim 40 nucleic acid molecules and their target nucleic acids. Thus, the non-specific effects produced by antisense molecules would be greatly reduced for the molecules of claim 40.

2. Branch

The rejection relied on Branch to show that the field of antisense oligomers is not predictable that there are non-specific toxic effects of *in vivo* antisense administration (page 5, Office Action, July 29, 2003). Branch involves antisense oligonucleotides, not nucleic acid molecules having endonuclease activity, and thus is not directly relevant to claim 40. Furthermore, Branch was published in 1998, approximately 3 years before the February 8, 2001 date of the present application, and is thus not clearly indicative of the state of the art at the time the present application was filed.

The discussion in Branch is focused on whether antisense molecules can cure a disease. As established above, this is not the standard by which enablement of pharmaceutical compositions is to be judged. Disregarding this, the rejection specifically relies on this erroneous standard, quoting Branch: "the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curves and therapeutic index is available"[7] (page 5, Office Action, July 29, 2003). Whether the antisense molecules or Branch or the nucleic acid molecules of claim 40 are safe, effective therapies is not indicative of whether the use of such molecules are enabled under 35 U.S.C. 112, first paragraph. For at least this reason, Branch does not provide evidence supporting a lack of enablement for claim 40.

In fact, Branch provides support for enablement of the molecules of claim 40. Branch states that "[a]lthough questions of their ultimate specificity remain, there is growing evidence that antisense molecules can be useful pharmacological tools when applied carefully." Branch,

[7] This quotation in the rejection implies that, to be enabled, a therapeutic molecule must go through the complete clinical trial procedure, Phase I, Phase II, Phase III, and Phase IV (which would have to be completed before the "dose response curves and therapeutic index" would be known) before it would be enabled, which is clearly not the state of the law.

p. 50, col. 1. Thus, even under the erroneously high standard, Branch indicates that antisense molecules would work.

Lastly, the Examiner has focused, as Branch did, on the "non-antisense" effects of antisense and how this creates unpredictability. However, in numerous places, Branch indicates that this actually will help the pharmaceutical activity of the antisense. For example, Branch states, "Non-antisense effects are not necessarily bad. Indeed, some may prove to be a boon to the pharmaceutical industry because they offer an added source of potency." Branch, p. 45, col. 2). As much as Branch tries to be a doomsday for the field, Branch still rightfully admits that there is success within the field, and when viewed through the appropriate standard of *any* activity *in vivo*, Branch clearly supports the enablement of claim 40.

3. Gewirtz

The rejection relied on Gewirtz to show that the field of antisense oligomers is not predictable. Gewirtz involves antisense oligonucleotides, not nucleic acid molecules having endonuclease activity, and thus is not directly relevant to claim 40. Furthermore, as with Branch, Gewirtz is stale since it was published in 1996, approximately four years before the priority date of the present application. In addition, Gewirtz focuses on clinical efficacy (which is not the relevant standard for enablement), but even at this early date, Gewirtz indicates that there was clinical success with antisense molecules (see discussion of c-myb antisense in page 3161, col. 2).

4. Agarawal

The rejection relied on the following quote from Agarawal: "[o]ligonucleotides must be taken up by cells in order to be effective . . . . several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is [a] complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum . . . ." It is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency." Applicants first note that this quote indicates that oligonucleotides *are* taken up in a variety of cells. This directly contradicts the assertions in the rejection that uptake of the antisense is at best unpredictable and at worst not possible.

Second, the quote does not even it say antisense are not taken up, the quote says, "negligible uptake." That means that, at worst, some uptake is still happening. Some uptake is all that enablement requires. Thus, the worst case scenario, for certain cells, according to Agarawal, still provides enough to meet the correct standard for enablement. Third, the rejection ends the quote with the statement "difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency." Respectfully, this is irrelevant to the correct legal standard for enablement of claim 40. Applicants do not have to enable the transfer of all oligonucleotides to all cells with the same efficiency. Applicants do not even have to enable a few oligonucleotides to some cells with the same efficiency. This statement by Agarawal lacks any bearing on the enablement of any antisense claim, much less bearing on the enablement of claim 40 as the statement has absolutely nothing to do with the correct standard and clearly indicates that it is directed to something else.

The rejection relied on another statement from Agarawal about the inefficiency of liposomal uptake. Again this statement supports the enablement of claim 40 by stating "[m]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture *increases* the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." Nowhere in claim 40 is it required that the claimed pharmaceutical compositions be delivered in vivo, this is a limitation added by the Examiner. Although use of the pharmaceutical compositions could involve delivery to cells in vivo, in vivo application of the claimed composition could also be accomplished via ex vivo technology.

Lastly, Agrawal provides evidence of human clinical trials with antisense oligonucleotides and this is evidence that therapeutic oligonucleotides meet a much higher standard than is required for enablement. Applicants' data merely need be suggestive of activity *in vivo*. Clearly, Agrawal indicates that Applicants' data would suggests far more than that.

5. Tamm

The rejection relied on Tamm for evidence of an alleged undesirable immune response by delivered antisense molecules. Tamm involves antisense oligonucleotides, not nucleic acid molecules having endonuclease activity, and thus is not directly relevant to claim 40. Furthermore, the properties of the claim 40 molecules as discussed above alleviate many of the

problems of the antisense world. As discussed below, Tamm clearly supports that antisense can work in vivo and that the claim 40 molecules would work also.

With respect to the reliance on Tamm for "[i]mmune stimulation is widely recognized as an undesirable side-effect . . . the immunostimulatory activity of a phophorothioate-modified oligonucleotide is largely unpredictable and has to be ascertained experimentally" (page 5, Office Action, July 29, 2003, citing Tamm page 493), this statement does not have anything to do with the enablement of the claim 40 molecules. The claim 40 molecules would be enabled even if every single molecule within the scope of the claim 40 caused the immune response such that the oligonucleotide could not be given again to the subject. The statement by Tamm goes to the ultimate success of the oligonucleotide as a therapy, but has nothing to do with the actual standard required for enablement. It may affect the amount of activity obtained in vivo, but this has nothing to do with the standard of enablement (which is does the molecule work at all). It may affect validation by the FDA, but this has nothing to do with the standard of enablement. It may effect whether the oligonucleotide would function in the market place, but again this has nothing to do with the standard of enablement.

Applicant also directs the PTO to a part of the quote from Tamm that the PTO left out of its argument highlighted by the ellipsis. The words immediately following the ellipsis state, "which can interfere with therapeutic activity" (Tamm, p. 493, col. 2). The very section of Tamm relied on in the rejection supports the enablement of claim 40 . . . if the PTO looked at the entire statement. The words "which can interfere with therapeutic activity" teach much. They teach first, that there is therapeutic activity contrary to the position taken by the PTO. Second, they teach that even when the deleterious effects of immunostimulation occur, these effects *can, not will or not must*, but can have an effect on the therapeutic activity. Third, they teach that the negative effects, if they occur, *interfere, not eliminate or not destroy*, but interfere, implying that the positive effects can still take place, albeit at an interfered level. In short, the section of Tamm supports the enablement of the claim 40 molecules.

Lastly, the majority of the Tamm reference discusses the clinical trials, and their success, of a number of antisense molecules (see Tamm, p. 491-493). Tamm clearly indicates that antisense oligonucleotides have activity in vivo, contrary to the position taken in the rejection.

Tamm discusses G3139 an antisense molecule for BCL2, and states, "[b]y day 5, daily doses of 1.7 mg/kg and higher led to a median decrease of BCL2 expression of 40% in melanoma samples compared to baseline. . . . . Based on the promising results of this study, the combination of dacarbazine and G3139 therapy in patients with malignant melanoma received fast-track approval by the FDA , and is in a phase III multicentre trial." (Tamm, p. 491, col. 2).

Tamm discusses ISIS 3521 which is an antisense to protein kinase C-alpha (PKC-alpha). Tamm states, "Results of a phase I study suggested that an antisense oligonucleotide directed against PKC-alpha (ISIS 3521) might be effective in the treatment of low-grade lymphoma." (Tamm, p. 491, col. 2). Tamm goes on to state, regarding a combination therapy with ISIS 3521, "thus, the combination of ISIS 3521, carboplatinm, and paclitaxel, was well tolerated, and showed promising activity in NSCLC [non-small-cell lung cancer]." (Tamm, p. 492, col. 1).

Tamm further discusses ISIS 5132, which is an antisense oligonucleotide directed to the 3' untranslated region of cRAF-1. Tamm states, "In a phase I trial, changes in cRAF-1 mRNA expression were analyzed in peripheral blood mononuclear cells collected from patients with advanced cancers treated with ISIS 5132. Significant reductions of c-RAF-1 expression from baseline were detected in 13 of 14 patients." (Tamm, p. 492, col. 1).

Tamm also discusses ISIS 2503, which is an antisense molecule directed to the human HRAS mRNA. In an interim analysis of a phase II study, Tamm states, "17 patients had received 38 cycles. Toxicity was limited to grade 1-2 fever and grade 1 thrombocytopenia in three patients. Two patients had stable disease after 3-6 cycles." (Tamm, p. 492, col. 2).

Tamm discusses c-Myb antisense oligonucleotides. Tamm indicates that in pilot studies of these antisense oligonucleotides in combination therapies, "four of six accessible patients with chronic myelogenous leukaemia, metaphases were 85-100% normal 3 months after engraftment, suggesting a huge purge in the marrow graft." (Tamm, p. 493, col. 1).

Tamm also discusses MG 98, an antisense inhibiting translation of DNA methyltransferase. Tamm states, "Biologically relevant concentrations for the inhibition of human DNA methyltransferase mRNA were achieved with the lowest dose assessed (40 mg/m3 daily)." (Tamm, p. 493, col. 1).

Tamm also discusses GEM 231, an antisense oligonucleotide targeting protein kinase A. Tamm states, "After oral or intraperitoneal administration, GEM 231 had dose-dependent in vivo antitumor activity in severe combined immunodeficient and nude mice bearing xenografts of human cancers of the colon, breast, and lung." ((Tamm, p. 493, col. 1). Tamm also states, "GEM 231 produces only mild and reversible side-effects." ((Tamm, p. 493, col. 2).

Thus, on the whole, Tamm clearly indicates that antisense oligonucleotides have activity in vivo, contrary to the position taken in the rejection.

With respect to the references that the rejection relies on, these references (1) are drawn to antisense molecules which are not clearly relevant to the molecules of claim 40, (2) any negative inference that can be taken from these references focuses on the wrong legal standard for enablement, a standard which is far higher than Applicants must meet, and (3) the references relied on in the rejection, when taken as a whole, clearly support the enablement of claim 40.

E. The Experimentation Required Is Not Undue

The rejection sets forth the "Wands" factors and sets the standard as "undue experimentation," but has incorrectly applied these factors to the specific technology at issue. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400 (Fed. Cir. 1988). The standard does not *disallow* experimentation. *Id.* The fact that experimentation may be complex does not necessarily make it undue, *if the art typically engages in such experimentation. M.I.T. v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 190 U.S.P.Q. 214 (CCPA 1976).

The facts underlying the decision of *In re Wands*, the benchmark case on enablement, illustrate well the concepts put forth in *MIT v. A.B. Fortia* and *In re Angstadt.* The method claims at issue in *Wands* involved the use of an antibody wherein the "antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for . . . [the antigen] of at least $10^9 M^{-1}$." *In re Wands*, 858 F.2d at 734. This claim covers *any* monoclonal antibody, not just a specific monoclonal antibody, and the PTO argued that the Applicant failed to enable *all* monoclonal antibodies. *Id.* The Federal Circuit found that the skilled artisan generates monoclonal antibodies by injecting an antigen into a host animal causing an immune reaction,

isolating spleen cells, some of which produce the antibodies that bind the antigen, fusing the spleen cells with a cancerous myeloma cell producing a hybridoma, and then screening individual hybridomas to isolate those that produce antibodies that bind the antigen. *Id.* at 733-734. The PTO supported its non-enablement position by pointing out that (1) not all hybridomas produce antibodies that bind antigen, (2) not all hybridomas that bind antigen will bind with an affinity of $10^9 M^{-1}$, and (3) the Applicants own data indicated that a small percentage of hybridomas actually produced monoclonal antibodies which fell within the scope of the claims. *Id.* at 738-739. The court rejected these arguments by stating:

> cell fusion [hybridoma technology] is a technique that is well known to those of skill in the monoclonal antibody art, . . .[t]here was a high level of skill in the art at the time when the application was filed, and all the methods needed to practice the invention were well known . . . [and] it seems unlikely that undue experimentation would be defined in terms of the number of hybridomas that were never screened, . . .[and since] Wands carried out his entire procedure three times , and was successful each time in making at least one antibody that satisfied all of the claim limitations . . . Wands evidence thus effectively rebuts the examiner's challenge to the enablement of their disclosure.

Id. at 740. Furthermore, the Wands court made clear that the amount of and type of experimentation considered undue fluctuates for each type of art. Id. The quantity of experimentation lacks relevance outside an assessment of what is "routine experimentation" in the art. *Id.* Thus, the huge amount of "experimentation" that the skilled artisan would have to perform to practice Wands' invention: immunizing an animal, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the hybridomas for the desired characteristics, knowing that many hybridomas would not produce functional antibodies and not knowing which hybridomas would produced claimed antibody, was not undue experimentation because it was routine experimentation in the art of monoclonal antibody production. *Id.* As discussed below, claim 40 and the corresponding enablement rejection closely parallel the situation presented in *Wands* since the art of producing

pharmaceutical compositions, assuming the applicant must specifically enable an in vivo pharmaceutical use, requires and routinely performs screening for activity, as evidenced by the evidence cited in the rejection. Thus, screening for activity in vivo, assuming that this is required, would be and is routine, and thus, the mere fact that screening would be performed does not make claim 40 non-enabled, even though it may seem complex.

F. The Specification Enables Routine Screening and the Identification of Active Ribozymes

The field of the nucleic acids of claim 40 is analogous to the field of antibodies in relevant ways. In both fields, the molecule of interest, an antibody or a nucleic acid molecule having endonuclease activity of claim 40 each may require screening to identify the molecule having the desired properties. This screening is routine. For example, Braasch states "it may be necessary to screen 20 or more oligomers before identifying one that functions properly" (Braasch, p. 4503, col. 2). This is minimal compared to antibodies, which as pointed out in *Wands*, may have hundreds of hybridomas screened to find the desired monoclonal antibodies. *Wands* at 738-739. The screening that may take place to isolate the pharmaceutical compositions of claim 40 is no different than the screening that would take place to isolate, for example, a therapeutic antibody, or an antibody having specific binding properties, which was already held not to be undue by the Federal Circuit in *Wands*.

As indicated by the specification and confirmed by the Examiner, in the publications relied on in the rejection, one of skill in the art understands what to do to make a functional nucleic acid work *in vivo*, and more importantly, they understand how to determine and screen for functional molecules *in vivo*. For example, the specification states "[a] pharmaceutically effective dose is that dose required to prevent, inhibit the occurrence, or treat (alleviate a symptom to some extent, preferably all of the symptoms) of a disease state. The pharmaceutically effective dose depends on the type of disease, the composition used, the route of administration, the type of mammal being treated, the physical characteristics of the specific mammal under consideration, concurrent medication, and other factors which those skilled in the medical arts will recognize." Page 24, lines 3-8. Clearly the skilled artisan understands how to

obtain an effective amount or determine if a particular functional nucleic acid is suitable for *in vivo* activity.

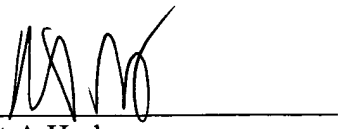
Not only does the specification make clear how to screen and test the claimed molecules, the publications relied on by the Examiner provide numerous examples of how to test a particular functional nucleic acid's *in vivo* activity (see Braasch, Branch, Agrawal, Tamm, and Gewirtz, all of which provide *in vivo* assays and activity profiles for a variety of enzymes, showing that these types of assays are well within the realm of the skilled artisan.).

In conclusion, Applicants respectfully request reconsideration and allowance of claim 40, as it is fully enabled the rejection of claim 40 under 35 U.S.C. § 112, first paragraph has been traversed.

A Credit Card Payment Form PTO-2038 authorizing payment in the amount of $210.00, representing the fee for a small entity under 37 C.F.R. § 1.17(a)(2), and an Amendment and Response to Office Action are enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.



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CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as attached or included, is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date indicated below.

Robert A. Hodges

12/29/2003
Date